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Dramatic Decline of Respiratory Illness Among US Military Recruits After the Renewed Use of Adenovirus Vaccines

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Background. In late 2011, after a 12-year hiatus, oral vaccines against adenovirus types 4 (Ad4) and 7 (Ad7) were again produced and administered to US military recruits. This study examined the impact of the new adenovirus vaccines on febrile respiratory illness (FRI) and adenovirus rates and investigated if new serotypes emerged. FRI rates and their associated hospitalizations had markedly risen since vaccine production ceased in 1999.

Methods. From 1996 to 2013, the Naval Health Research Center conducted FRI surveillance at 8 military recruit training centers in the United States. During this period, 58 103 FRI pharyngeal swab specimens were studied, yielding 37 048 adenovirus-positive cases, among which 64% were typed.

Results. During the 2 years after reintroduction of the vaccines, military trainees experienced a 100-fold decline in adenovirus disease burden (from 5.8 to 0.02 cases per 1000 person-weeks, $P < .0001$), without evidence that vaccine pressure had increased the impact of adenovirus types other than Ad4 and Ad7. Although the percentage of type 14 increased following reintroduction of the vaccination, the actual number of cases decreased. We estimate that the vaccines prevent approximately 1 death, 1100–2700 hospitalizations, and 13 000 febrile adenovirus cases each year among the trainees.

Conclusions. These data strongly support the continued production and use of Ad4 and Ad7 vaccines in controlling FRI among US military trainees. Continued surveillance for emerging adenovirus subtypes is warranted.

Keywords. adenovirus; febrile respiratory illness; military; surveillance; vaccine.

Adenovirus infections are very common among military trainees. This is thought to be due to the trainees' close living quarters, minimal time for personal hygiene, persistence of adenoviruses in the environment [1, 2], and the vigorous physical and environmental stressors of training camp. Before the adenovirus vaccines were routinely available, it was estimated that

80% of recruits became infected during recruit training, 40% had a significant illness, and 20% required hospitalization [3]. Due to the high burden of adenovirus disease, the Naval Health Research Center (NHRC) has conducted ongoing adenovirus surveillance among recruits at 8 recruit training centers since 1996, as part of the Department of Defense (DoD) febrile respiratory illness (FRI) surveillance program.

After a number of other vaccine constructs were tested, live oral vaccines against adenovirus types 4 (Ad4) and 7 (Ad7) were introduced in 1971 and were successful in greatly reducing respiratory morbidity at recruit training centers. In 1996, adenovirus vaccine manufacturing was halted when the sole manufacturer, Wyeth Pharmaceuticals, declined to continue production. When a military order rationed the remaining adenovirus vaccine

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stockpile to be used only during winter months from 1997 to 1999, adenovirus rates increased dramatically [4, 5]. Rates continued to escalate when vaccine supplies were depleted in 1999, after which the vaccines were no longer administered. The increased number of adenovirus infections cost approximately \$10–\$26 million per year in terms of medical care and lost recruit training time [6, 7]. During the period from 1999 to 2010, 8 adenovirus-infected recruits died [8, 9]. However, it is difficult to compare the vaccine and postvaccine mortality rates due to changes in surveillance and laboratory capabilities [8].

As it became clear that adenovirus infections had again become highly endemic in US recruit training centers, the US Army contracted with Barr Pharmaceuticals in 2001 to resume production of the Ad4 and Ad7 vaccines. Phase 3, double-blind, placebo-controlled clinical trials of the 2 vaccines were conducted by the US Navy and Army at recruit training sites in Fort Jackson, South Carolina, and the Recruit Training Command (RTC) at Naval Station Great Lakes, Illinois. Results from this trial demonstrated that Ad4 vaccine had a very high efficacy (99%), and Ad4 and Ad7 vaccines had high seroconversion rates and excellent safety profiles [10].

Following US Food and Drug Administration approval in March 2011, universal administration of Ad4 and Ad7 vaccines at all US recruit training sites resumed in October 2011. The purpose of this study was to assess the effectiveness of the new Ad4 and Ad7 vaccines in reducing FRI among recruits and to determine whether new strains emerged.

METHODS

Participants

FRI surveillance took place at 8 military recruit training facilities across the United States from 1996 to 2013. The sites included RTC Great Lakes; Marine Corps Recruit Depot (MCRD) San Diego, California; MCRD Parris Island, Parris Island, South Carolina; Air Force Basic Military Training Center, Lackland, Texas; Army Basic Combat Training Center, Fort Leonard Wood, Missouri; Army Basic Combat Training Center, Fort Jackson, South Carolina; Army Basic Military Training Center, Fort Benning, Georgia; and the Coast Guard Training Center (CGTC), Cape May, New Jersey. In 1996, the only sites being surveilled were MCRD San Diego and RTC Great Lakes.

Recruit training generally lasts from 6 to 12 weeks, depending on service branch. “Boot camp” is physically demanding and recruits are in close contact throughout the day and night, living in high-density barracks. During the first week of training, recruits are typically given a series of vaccinations. From the 1970s to 1996, Ad4 and Ad7 vaccines were included in year-round vaccinations, from 1997 to 1999 these vaccines were only given during winter months, and from 2000 to 2011 they were not administered at all. Starting in October and November of 2011,

adenovirus vaccination was resumed, and by 2012 year-round vaccination was once again given to all incoming recruits.

Procedures

Each week an on-site NHRC research staff member collected data on the number of FRI cases and total recruit population at each recruit training site, with the exception of the relatively small Cape May CGTC, where clinic staff provided the data. An FRI case was defined as a recruit who sought medical care and had an oral temperature $\geq 38^{\circ}\text{C}$ (100.5°F) and either cough or sore throat. Pharyngeal or combination nasal/pharyngeal swabs and questionnaire data were collected from a convenience sample of up to 20 recruits per week per site who sought medical attention, met the FRI case definition, and provided written informed consent. Specimens were placed in viral transport medium, preserved at -80°C , and later transported on dry ice to the reference laboratory at NHRC every 1–2 weeks for testing.

From 1996 to 2004, viral culture in A549 cells was used to identify adenovirus-positive cases, and serotyping was performed on a subset of 10%–30% of positive specimens by microneutralization (MN) assay [4]. Starting in mid-2004 through 2006, initial adenovirus identification was determined by molecular methods, and the MN assay described above was used to serotype approximately 20% of positive specimens. Beginning in 2007, a single-plex, gel-based polymerase chain reaction (PCR) assay [4] was used to test specimens for adenovirus species B, C, and E. Specimens positive for species E were classified as Ad4, and species B and C adenovirus specimens were further tested by type-specific PCR assays to determine serotype. In late 2010, testing for adenovirus was transitioned to a real-time PCR assay, and all positive samples were serotyped by PCR methods as previously described. Despite the different laboratory methods used for our study, our laboratory found 90%–96% agreement when comparing viral culture and PCR results from thousands of FRI samples.

Statistical Analysis

Annual FRI incidence rates were calculated by dividing the number of cases by the total person-weeks at all sites. Person-weeks were computed by summing the number of recruits for each week at all sites. Estimated annual adenovirus incidence rates were calculated by multiplying the percentage of specimens positive for adenovirus by the FRI rate. The estimated number of adenovirus cases was determined by multiplying the adenovirus rate by person-weeks for each site and summing all of the sites to get the total number for each year. In 1998, the estimated number of adenovirus cases was extrapolated from the existing surveillance data from June through December by assuming the number of cases was constant throughout the year. The number of hospitalizations per year was calculated by multiplying the estimated annual number of adenovirus

cases by historical rate estimates for adenovirus hospitalization, which ranged from approximately 8% to 20% [3, 6, 11].

Data were grouped by vaccination period: year-round vaccination (1996), seasonal vaccination in winter months (1997–1999), no vaccination (2000–2011), and year-round vaccination (2012–2013). Differences of FRI and adenovirus rates across vaccination periods were assessed using Poisson regression, and differences of mean estimated number of adenovirus cases were assessed using analysis of variance (ANOVA), with $P < .05$ considered significant. The PROC GENMOD procedure with a log link was used for the Poisson regression analyses, and the PROC ANOVA procedure was used for the ANOVA analysis. SAS version 9.3 was used.

Ethics

This research was conducted in compliance with all applicable federal and international regulations governing the protection of human subjects in research (DoD protocols NHRC 31230 and NHRC.1999.0002).

RESULTS

From 1996 to 2013, NHRC collected and tested 58 103 FRI swab specimens, of which 37 048 (64%) were positive for adenovirus.

During this time, NHRC typed on average 61% (range, 9%–100% annually) of adenovirus-positive specimens to identify the most prevalent strains. The proportion of adenovirus-positive cases serotyped was lower prior to 2007 due to the use of MN characterization techniques that were labor intensive in comparison with PCR.

As vaccination policies changed throughout the course of surveillance, large fluctuations in both FRI and adenovirus rates were observed. FRI and adenovirus rates followed a similar pattern, peaking during the nonvaccination periods (8.5 FRI cases per 1000 person-weeks; 5.8 adenovirus cases per 1000 person-weeks) and dropping when vaccination resumed (1.2 FRI cases per 1000 person-weeks, 0.02 adenovirus cases per 1000 person-weeks) (Table 1). Annual site-specific adenovirus rates varied across the sites, with peaks during the nonvaccination period between 6.5 and 21.0 adenovirus cases per 1000 person-weeks. During this time, high levels of adenoviral morbidity were observed at all sites, with maximum estimated annual adenovirus cases ranging from 605 at the smallest training center (CGTC Cape May) to 5880 at RTC Great Lakes. From 2012 to 2013, the maximum number of site-specific estimated adenovirus cases was 45 (Table 2). The mean estimated number of adenovirus cases per year was 13 518 during the nonvaccination period, 6504 during the rationed years, and 60 after resumption

Table 1. Characteristics of Adenovirus and Febrile Respiratory Illness as Vaccination Policy Changed, 1996–2013

Characteristic	Year-round Ad4 and Ad7 Vaccines Administered (1996 ^a)	Seasonal Ad4 and Ad7 Vaccines Administered (1997–1999)	No Ad Vaccines Administered (2000–2011)	Year-round Ad4 and Ad7 Vaccines Administered (2012–2013)	<i>P</i> Value ^b
Average No. tested per y	201	3310	3990	1725	
% Ad positive	11.9	57.2	67.6	4.7	
FRI rate (95% CI) ^c		5.8 (5.7–5.9) ^d	8.5 (8.4–8.5)	1.2 (1.1–1.2)	<.0001
Ad rate (95% CI) ^c		3.4 (3.3–3.4) ^d	5.8 (5.8–5.8)	0.02 (.02–.02)	<.0001
Mean (SD) No. estimated Ad cases per y		6504 (3737) ^d	13 518 (2786)	60 (42)	<.0001
% Serotyped	100	56	61	100	
Ad species/type (% of total serotyped)					
C/1	0	0	0	2	
C/2	25	1	0	1	
B/3	4	7	2	2	
E/4	4	65	80	9	
C/5	0	1	0	1	
B/7	4	20	2	1	
B/14	0	0	10	54	
B/21	58	6	2	0	
Other/unknown	4	0	4	30	

Abbreviations: Ad, adenovirus; CI, confidence interval; FRI, febrile respiratory illness; SD, standard deviation.

^a Marine Corps Recruit Depot San Diego and Great Lakes Recruit Training Command were the only sites in 1996.

^b *P* value is for significant rate or mean difference across 3 time periods: seasonal vaccines (1997–1999), no vaccines (2000–2011), and year-round vaccines (2012–2013).

^c No. of cases per 1000 person-weeks.

^d Only includes data from June 1998 to December 1999 (adjusted to estimate full year for 1998).

Table 2. Estimated Adenovirus Cases Annually by Site, 2000–2011 and 2012–2013

Site	No Ad Vaccines Administered 2000–2011, Mean (SD)	Year-round Ad4 and Ad7 Vaccines Administered 2012–2013, Mean (SD)
Fort Leonard Wood	1453 (510)	5 (5)
Fort Jackson	2667 (900)	4 (0)
Fort Benning	1493 (729)	8 (1)
RTC Great Lakes	3968 (1147)	12 (12)
MCRD San Diego	1312 (846)	3 (1)
MCRD Parris Island	942 (480)	27 (26)
Lackland AFB	1507 (1219)	1 (1)
CGTC Cape May	177 (153)	0 (0)

Abbreviations: Ad, adenovirus; AFB, Air Force Base; CGTC, Coast Guard Training Center; MCRD, Marine Corps Recruit Depot; RTC, Recruit Training Command; SD, standard deviation.

of year-round vaccination (Table 1 and Figure 1). During the nonvaccination period, approximately 1100–2700 adenovirus hospitalizations occurred annually, and in 2012 and 2013 approximately 5–12 hospitalizations occurred with no documented deaths.

In 1996, the last year adenovirus vaccines were given to recruits year-round, Ad21 was the most prevalent type, comprising 58% of typed specimens, whereas Ad4 and Ad7 were only 4% each of all typed viruses. However, when vaccines were

rationed from 1997 to 1999, Ad4 and Ad7 reemerged as the most prevalent types, comprising 65% and 20% of all viruses typed, respectively. Ad4 rose even further to 80% of typed viruses during 2000 to 2011, with the remaining 20% comprising the diverse serotypes Ad14, Ad21, Ad3, Ad7, and other/unknown types, when no vaccines were given. However, after vaccines were reintroduced, Ad4 and Ad7 declined to 9% and 1% of typed viruses, respectively (Table 1). During 2012, there were only 5 cases positive for Ad4p (the vaccine strain) and no cases positive for Ad7. The incidence of other adenovirus serotypes has also declined since the vaccine was resumed; for Ad14, the most prevalent nonvaccine adenovirus type, the estimated mean annual number of cases decreased from 610 in 2000–2011 to 44 in 2013.

DISCUSSION

With year-round adenovirus vaccination resumption in 2012, adenovirus infections decreased by approximately 100-fold among US military recruit trainees. Besides preventing unnecessary fatalities, adenovirus vaccines in the recruit population can prevent approximately 13 000 acute febrile illnesses a year and the associated lost training time and healthcare costs. As seen in previous years, even a short relapse or reduction in vaccination has resulted in serious adenovirus outbreaks and several deaths among military trainees [8, 9, 12–14]. Reestablishing production of the orphaned Ad4 and Ad7 vaccines was a costly

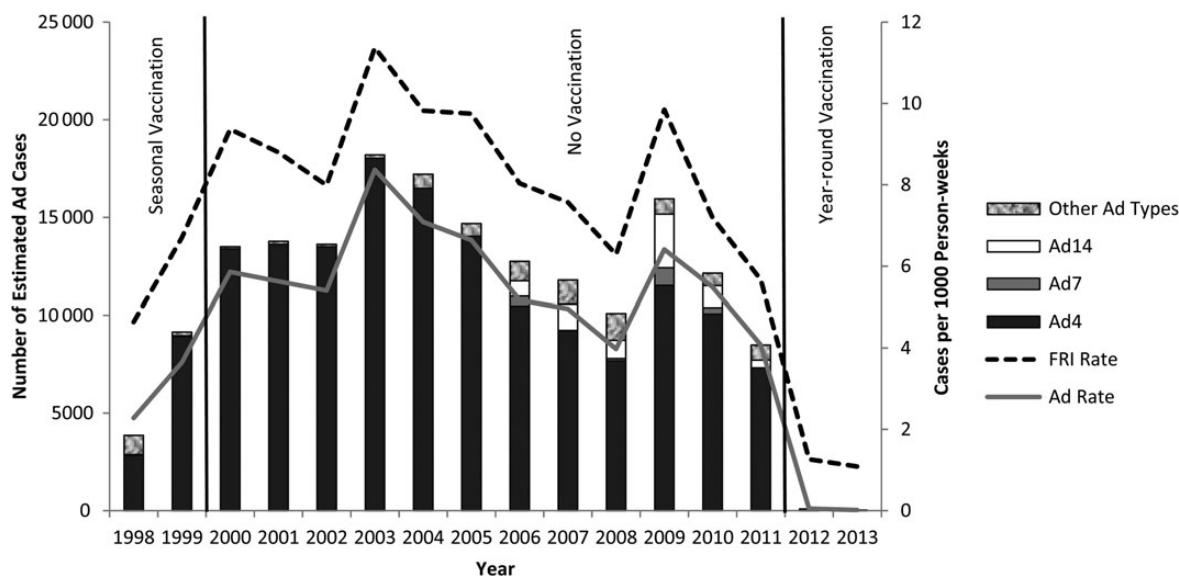


Figure 1. Febrile respiratory illness and adenovirus rates per 1000 person-weeks and number of estimated adenovirus cases (types 4, 7, 14 and other) per year, 1998–2013. Three vaccination time periods were observed: seasonal vaccination during winter months (1998–1999), no vaccination (2000–2011), and year-round vaccination (2012–2013). Abbreviations: Ad, adenovirus; FRI, febrile respiratory illness.

Table 3. Average Cost Estimates Associated With Adenovirus Vaccines and Adenovirus Illness per Military Recruit

Variable	Cost in 1995 [7]	Cost in 2012
Vaccine cost (Ad4 and Ad7)	\$15 ^a	\$150
Illness-related costs		
Training costs (3 d)	\$471	\$710 ^b
Medical costs	\$1663	\$3128 ^c
Total	\$2134	\$3838

Abbreviation: Ad, adenovirus.

^a Includes administrative costs and US Department of Defense Personnel Support Center surcharge.

^b Adjusted for inflation using the US Consumer Price Index for All Urban Consumers (all items) [16].

^c Adjusted for inflation using the US Consumer Price Index for all Urban Consumers (medical care item) [16].

and lengthy endeavor—the US government invested approximately \$107 million over 10 years to reinstate the 2 vaccines [15]. Ensuring continued vaccine production and sufficient supplies for uninterrupted, year-round vaccination of all recruits should be a public health and fiscal priority for US DoD trainees in the future. Similarly, these vaccines could significantly reduce FRI and adenovirus rates in other foreign military recruits and police trainees who have also experienced adenovirus outbreaks and high burden of disease [16–20]. These vaccines also have the potential to reduce transmission to other geographical locations and to civilians after recruits have completed training and disperse globally [21].

After adjusting 1995 cost estimates associated with adenovirus infection [7] using the US Consumer Price Index for all Urban Consumers (all items and medical care item) [22], we estimated that each adenovirus infection costs approximately \$3838 (\$3128 for medical costs and \$710 for lost training costs) in 2012 (Table 3). With approximately 13 000 clinical adenovirus illnesses prevented annually by year-round vaccination, the DoD would save approximately \$50 million per year. During the first few years, the price of the new vaccines ranged from \$120 to \$150 per person for the 2 doses. Vaccinating approximately 200 000 new recruits a year at \$150 per person for the 2 doses would cost \$30 million, providing a net savings of approximately \$20 million. The annual cost savings of the new adenovirus vaccines is slightly higher than previous estimates of \$15–\$16 million for the old vaccines [7]. However, this cost savings is still an underestimate, as it does not include the cost associated if a recruit must restart the training program, and it does not include the difficult-to-measure cost and burden of a death.

In contrast to our surveillance findings, 2 cost-benefit studies did not predict an increased benefit of year-round adenovirus vaccination compared with seasonal vaccination during winter months [6, 7]. A study by Hyer et al estimated that year-round

vaccination would prevent only an additional 540 cases compared with no vaccination [6]. Similarly, a study by Howell et al estimated that both seasonal and year-round vaccination would prevent approximately the same number of cases [7]. The study by Hyer et al used prevaccination data from 1949 to 1966 that found higher rates in winter months [6]. However, our more recent surveillance data showed that FRI and adenovirus rates were higher in summer and fall months, which have been explained by a correlation with higher recruit populations during this time [5]. Consequently, our data showed that year-round vaccination prevented approximately 6000 and 13 000 additional adenovirus cases compared with seasonal and no vaccination, respectively. These results support the importance of the current year-round vaccination policy and explain the ineffectualness of the previous seasonal vaccination policy that administered vaccines only in winter months.

Our surveillance data had similar burden-of-disease estimates for nonvaccination years and seasonal vaccination years as previous studies predicted. The study by Howell et al estimated that 12 370 cases would occur during years without vaccination and 4570 cases would occur during both seasonal targeted vaccination and year-round vaccination of recruits [7]. We found an estimated 13 518 cases per year during the nonvaccination period, and 6504 cases per year during the seasonal vaccination period. However, unlike Howell et al, we only saw an estimated 60 cases per year during year-round vaccination from 2012 to 2013 (Table 1). This may be a result of the new adenovirus vaccine being a better match to the current circulating strains, at least at present.

After 25 years of year-round Ad4 and Ad7 vaccination, other adenovirus types were present in the recruit training population. NHRC's limited sampling in 1996 demonstrated the presence of 3 nonvaccine adenovirus types, the majority of which were isolated from the RTC Great Lakes [4]. When vaccine became seasonal or nonexistent, Ad4, a vaccine component, emerged as the predominant strain. In 2006, during the nonvaccination period, Ad14 suddenly emerged in 5 recruit training sites and became the most prevalent non-Ad4 subtype [23]. During the next 4 years, Ad14 became the most predominant type for prolonged periods at 4 of the 8 sites (data not shown). When vaccination resumed in 2012, Ad4 decreased significantly, supporting the effectiveness of the vaccine in preventing Ad4. During 2012 to 2013, Ad14 supplanted Ad4 as the most prevalent strain overall, although the estimated annual cases of Ad14 have also decreased markedly (98% reduction) (Table 1 and Figure 1). The decline of estimated annual cases of Ad14 and other types may be reflective of cross-reactive antibodies from the vaccines [24] and overall reduced persistence in the environment or a result of natural variances. As year-round vaccination continues, it will be important to monitor potentially emerging strains through established surveillance systems to see if rates of nonvaccine strains change.

An important strength of this study is that it included >18 years of data from 8 recruit sites throughout the country with continued observation during times of vaccination policy change. The size of the surveillance population, as well as the number of FRI and adenovirus specimens collected and tested, was consistent from year to year, with the exception of 1996 when the surveillance program was started. This consistency made for a robust surveillance system that allowed for comparability across the years. Additionally, our study included type-specific data, allowing assessment of temporal changes in strain predominance.

Despite the large scale of this surveillance program, it is difficult to capture the total number of recruits with FRI as not everyone with symptoms seeks medical attention. Many recruits with symptoms may also avoid seeking medical attention because it may prolong their training or cause them to be removed from service, or because they may be placed in a holding facility [5]. Previous studies have found that approximately one-third of recruits entered training with Ad4 immunity, one-third seroconverted with few symptoms and without a fever, and one-third had a febrile infection [2, 25]. By the end of the sixth week of training, 97% of all recruits had positive adenovirus titers [2]. Therefore, the estimated adenovirus burden and associated costs in this study are likely underestimated. Additionally, changes in healthcare-seeking behavior may also bias results. In 2009, the increase in cases of both adenovirus and FRI (Figure 1) was likely caused in part to more recruits going to clinics when they were sick due to worry about the 2009 H1N1 influenza pandemic. However, adenovirus rates during this year were within the range seen in other years during the no-vaccination period.

Previous studies have shown that adenovirus vaccination is the only dependable prevention measure for adenovirus infection in this population. Hand-washing was found to be protective, but compliance was difficult to enforce [26], and other environmental controls, such as reducing recruit density per barrack, were not effective [27]. The new adenovirus vaccines have an excellent safety profile and high effectiveness [10]; after full resumption of the vaccines in all recruits in 2012–2013, adenovirus rates plummeted from 5.8 to 0.02 cases per 1000 person-weeks. Therefore, year-round vaccination should continue as the first line of defense against adenovirus infection in US military recruits and vaccine production should continue. NHRC's ongoing surveillance will monitor FRI and adenovirus rates in the future, paying particular attention to any rate increases of adenovirus types not included in the vaccines. This surveillance is important to assess ongoing vaccine effectiveness among military recruits.

Notes

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14. ABSTRACT <p>Background. In late 2011, after a 12-year hiatus, oral vaccines against adenovirus types 4 (Ad4) and 7 (Ad7) were again produced and administered to US military recruits. This study examined the impact of the new adenovirus vaccines on febrile respiratory illness (FRI) and adenovirus rates and investigated if new serotypes emerged. FRI rates and their associated hospitalizations had markedly risen since vaccine production ceased in 1999.</p> <p>Methods. From 1996 to 2013, the Naval Health Research Center conducted FRI surveillance at 8 military recruit training centers in the United States. During this period, 58 103 FRI pharyngeal swab specimens were studied, yielding 37 048 adenovirus-positive cases, among which 64% were typed.</p> <p>Results. During the 2 years after reintroduction of the vaccines, military trainees experienced a 100-fold decline in adenovirus disease burden (from 5.8 to 0.02 cases per 1000 person-weeks, $P < .0001$), without evidence that vaccine pressure had increased the impact of adenovirus types other than Ad4 and Ad7. Although the percentage of type 14 increased following reintroduction of the vaccination, the actual number of cases decreased. We estimate that the vaccines prevent approximately 1 death, 1100–2700 hospitalizations, and 13 000 febrile adenovirus cases each year among the trainees.</p> <p>Conclusions. These data strongly support the continued production and use of Ad4 and Ad7 vaccines in controlling FRI among US military trainees. Continued surveillance for emerging adenovirus subtypes is warranted.</p>					
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